A review on human reinstatement studies: An overview and methodological challenges

Running title: Review of Human reinstatement studies

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ABSTRACT

In human research, return of fear (ROF) phenomena and reinstatement in particular, have only begun to be studied a decade ago and are recently more widely used e.g. as outcome measures for fear/extinction memory manipulations (e.g. reconsolidation). As reinstatement research in humans is still in its infancy, providing an overview of its stability and boundary conditions and summarizing methodological challenges is timely to foster fruitful future research. As a translational endeavor, clarifying the circumstances under which (experimental) reinstatement occurs may offer a first step towards understanding relapse as a clinical phenomenon and pave the way for the development of new pharmacological or behavioral ways to prevent ROF. The current state of research does not yet allow pinpointing these circumstances in detail and we hope that this review will aid the research field to advance in this direction.

As an introduction, we begin with a synopsis of rodent work on reinstatement and theories that have been proposed to explain the findings. The review however mainly focuses on reinstatement in humans. We first (1) describe details and variations of the experimental set-up in reinstatement studies in humans and give a general overview over results. We continue with (2) a compilation of possible experimental boundary conditions and end (3) with the role of individual differences and behavioral and/or pharmacological manipulations. Furthermore, we (4) compile important methodological and design details on the published studies in humans and end with (5) open research questions and some important methodological and design recommendations as a guide for future research.

INTRODUCTION

Learning to predict danger from the environment (*fear conditioning* in experimental terms) as well as learning when these environmental contingencies change is critical for adaptive behavior. The latter, referred to as *extinction*, does in most circumstances not erase conditioned fear memories (conditioned stimulus [CS] – unconditioned stimulus [US] association), but generates competing, fear-inhibitory extinction memories (CS- no US) both of which co-exist after successful extinction (Bouton, 2004; Myers & Davis, 2007). Insufficient expression of extinction memories upon re-confrontation with a conditioned stimulus (CS) results in return of fear (ROF), which represents a likely basis of relapse that occurs after successful extinction-based cognitive behavioral therapy (CBT) (for an overview see e.g. Vervliet, Craske, & Hermans, 2013). ROF can be experimentally induced in the laboratory following successful extinction through the mere passage of time (*spontaneous recovery*), induction of contextual change (*renewal*) or by exposure to unsignaled USs (*reinstatement*) (for an overview in animals: Bouton, 2004; in humans: Vervliet, Craske, & Hermans, 2013).

Reinstatement was first described in animals by Pavlov (Pavlov, 1927), studied further by Rescorla (Rescorla & Heth, 1975; Rescorla & Cunningham, 1977) and was systematically investigated in rodents by Bouton and collegues (e.g. Bouton & Bolles, 1979; Bouton & King, 1983; Bouton, 1984). In human research, ROF phenomena and reinstatement in particular, have only begun to be studied a decade ago and have recently begun to be more widely used e.g. as outcome measures for fear/extinction memory manipulations. As reinstatement research in humans is still in its infancy, providing an overview of the reliability and possible boundary conditions of this phenomenon and summarizing methodological challenges is timely to foster fruitful future human research. As a translational endeavor, clarifying the circumstances under which (experimental) reinstatement occurs may offer a first step towards

understanding relapse as a clinical phenomenon and pave the way for the development of new pharmacological or behavioral ways to prevent ROF.

Currently however, our knowledge of experimental boundary conditions as well as biological or trait factors for reinstatement is very limited in humans and methodological work is critically needed. Therefore, we focus herein on the reports of reinstatement in humans un-confounded by other experimental manipulations (e.g. reconsolidation, drugs etc.). The systematic overview of human work provided in this review represents a first step along this avenue and will hopefully aid the research field to advance and grow. For introductory purposes and to allow the reader to put the human work into a bigger context, we also provide an overview of mechanisms and theories derived from rodent work that have been put forward to explain the reinstatement phenomenon.

We begin the review of human reinstatement literature with (1) a general summary of details and variations of the experimental set-up in reinstatement studies in humans and review reinstatement effects in the literature. We continue with (2) a comprehensive compilation of possible experimental boundary conditions and methodological details in human work and end (3) with the role of individual differences and behavioral and/or pharmacological manipulations in humans. Additionally, we provide (4) a tabular compilation of important methodological and design details on the published studies in humans throughout the manuscript. In closing, we discuss open research questions and (5) derive methodological and design recommendations as a guide for future human studies. The latter is of paramount importance as a comprehensive characterization, clean study design as well as a uniform statistical tests to evaluate reinstatement effects in humans is needed to advance a more comprehensive understanding of this important phenomenon.

A synopsis of rodent work on reinstatement and their mechanistic implications

Reinstatement has first been described nearly a century ago (Pavlov, 1927) but only decades later, Rescorla and colleagues (Rescorla & Heth, 1975; Rescorla & Cunningham, 1977) used the reinstatement phenomenon to demonstrate that extinction does not result in erasure of the originally learned association.

Rescorla demonstrated that re-exposure to the US after extinction reinstates fear even when the US was predicted by a CS as well as when reinstatement US presentations and test were separated in time (Rescorla & Heth, 1975). These phenomena were interpreted as a re-strengthening of the US representation (Rescorla & Heth, 1975; Rescorla & Cunningham, 1977). The theory (Rescorla, 1979) grounding on these results was later introduced as *a release from inhibition* may underlie the reinstatement phenomenon. During extinction the "CS+-US association" is thought to be inhibited by formation of an "extinction context – no US" memory that "masks" the original learning (Rescorla, 1979). Re-exposure of the US during reinstatement (in the inhibitory extinction context) un-masks or restores the excitatory CS-US association consequently leading to reinstatement at test in the same context. In other words, the extinction context acquires the ability to enhance the threshold at which the CS-US association is activated during extinction and US-alone re-exposure during reinstatement reduces this threshold, which subsequently leads to ROF to previously extinguished CSs (Robert A. Rescorla & Cunningham, 1977; Robert A. Rescorla, 1979). The above prediction is however only valid when extinction, reinstatement and test context are identical, as commonly done in these early studies. Thus, this theory has later been abandoned, when it was shown that it is sufficient to observe reinstatement that reinstatement and test context were identical (Bouton & Bolles, 1979; Bouton & King, 1983; Bouton & Peck, 1989).

The role of the reinstatement context and its excitatory properties was established by Bouton and colleagues in a series of experiments (e.g. Bouton & Bolles, 1979; Bouton & King, 1983; Bouton, 1984; Frohardt et al., 2000). The amount of reinstatement was, for example, correlated with the amount of context conditioning the animals displayed at the start of the

test session (Bouton & King, 1983 [Exp. 2]; Bouton, 1984). Also, rodents that were extinguished to the reinstatement context after reinstatement but before CS presentations at test, did not show reinstatement to the CS in this context (Bouton & Bolles, 1979; replicated in Westbrook et al., 2002). In addition, no reinstatement was observed when reinstatement took place in a novel or the original conditioning context and the similarity to the extinction context seemed irrelevant in this scenario (Bouton & King, 1983 [Exp. 2]).

In sum, the work by Bouton and colleagues suggests that reinstatement to a CS depends on conditioning to the reinstatement context. Two hypotheses have been put forward to explain these findings: First, the *summation hypothesis*, which bends to the Rescola-Wagner model and views the context as a stimulus whose excitatory or inhibitory association with the US sums up with that of the CS and the US (Rescorla & Wagner, 1972; Bouton & Bolles, 1979; Bouton & King, 1983 [Exp. 2]). This hypothesis suggested that the remaining excitatory value of the CSs after extinction is summed with the excitatory value of the newly conditioned context (the reinstatement context). Contrary to predictions however, results were specific for extinguished stimuli, as only these were affected by context conditioning through reinstatement, while responses to unextinguished CSs were not further enhanced (Bouton & King, 1986). In addition, results for partially reinforced stimuli (Bouton & King, 1986; Bouton, 1984) were a challenge to this hypothesis and as a result of these limitations, Bouton rejected this hypothesis in favour of the *retrieval model*. According to this model, the context functions as an "occasion setter". Contextual fear generated by reinstatement USs gates retrieval of the latent "CS-US association" (acquisition memory, context independent) over the competing "CS no-US" association (extinction memory, context dependent) resulting in ROF (Bouton, Rosengard, Achenbach, Peck, & Brooks, 1993; Bouton, 2004). According to this approach, extinction and acquisition memory co-exist after extinction and conditioned responding at test is determined by the dominance of one over the other. Observations of more pronounced ROF when test and reinstatement context are identical is in line with this

theory as well as the absence of ROF when the reinstatement context was extinguished following reinstatement US presentation (Bouton & Bolles, 1979; replicated in Westbrook et al., 2002). The retrieval model is able to explain most of the circumstances when ROF is observed in rodents and still represents the prevailing explanation. Some findings however challenge this theory. For example, reinstatement occurs when reinstatement and test context are different, provided that the reinstatement and the extinction context are identical (Westbrook et al., 2002 [Exp. 2b]). Reinstatement in this experimental design was enhanced beyond renewal effects [Exp. 3] and was strongest for a CS which's corresponding extinction context served as the reinstatement context [Exp. 4] (Westbrook et al., 2002).

Westbrook and colleagues re-visited the hypothesis of *mediated conditioning* (Holland, 1981), in an attempt to explain their findings. They propose an additional function of context conditioning in reinstatement, beyond associations with the US: During extinction, the CS becomes associated with the corresponding context and after reinstatement the US also becomes associated with this context. Through this common association of the "CS and the context" and the "context and the US", reinstatement is mediated through new contextual learning. A similar explanation represents the *associative chaining* framework (Hall, 1996): Through the common association outlined above (CS – context and context - US), the extinguished link between the CS and the US can be renewed during test via CS presentation which activates the representation of the context and thereby also of the US. The theories of mediated conditioning and associative chaining differ from each other only with respect to when the context links the extinguished CS to the US. Nevertheless, the hypothesis of mediated conditioning cannot explain ROF that is observed when US re-exposure took place in a novel context that was never associated with the CS (no common association between the CS – context – US) and then tested in a different, novel context (Westbrook et al., 2002 [Exp. 3, group BC]). However, based on the retrieval model, response enhancement in this experimental design may be explained by a generalization of fear from the conditioned

reinstatement-context to the test context that goes beyond renewal (as discussed in Westbrook et al., 2002).

One attempt to model these results derived from rodent studies as well as one human study (LaBar & Phelps, 2005), resulted in the *attentional-associative model* (Schmajuk, Larrauri, & Labar, 2007). According to this model, the CS and the context compete for attention with the US. Due to the discrete presentations of the CS, a strong CS-US association, but only a weak context-US association is formed during acquisition. During extinction, the context-US associations acquire inhibitory properties and the CS-US association remains intact. In addition, attention to the context and the CS decreases during extinction, until the presentation of the US during reinstatement increases attention to the context (due to the lack of a present CS). This enables the formation of an excitatory context-US association, as well as an attentional shift to the CS during test. When reinstatement and test occur in the same context, reinstatement was proposed to result from decreased contextual inhibition and increased attention to the CS, leading to a re-activation of the CS-US association. When reinstatement occurred in the extinction context and the CS was tested in a context different from that, reinstatement resulted from enhanced attention to the CS and re-activated CS-context and context-US associations.

Interestingly, Pearce and Hall (Pearce & Hall, 1980) already proposed that processes of attention are necessary to enable associative learning and that attention is a function of experience (Pearce & Bouton, 2001 [for a review] ; Pearce & Hall, 1980). According to the model, learning declines if the event following the CS is completely predicted by the CS. This model accounts for the assumptions in the former model of low attention to the CS and the context at the end of extinction, as well as the enhanced association of the context with the unexpected presentation of the US during reinstatement.

The theoretical frameworks for reinstatement outlined above are not mutually exclusive as multiple mechanisms that underlie reinstatement processes might act in compound or in

isolation, depending on the specific experimental design and demand (e.g. similarity of extinction, reinstatement and test context). If extinction occurs in one context, which is different from the context of reinstatement and test (which in turn are identical), reinstatement can be explained by a retrieval of the CS-US association elicited by the conditioned context (Bouton & Bolles, 1979; Bouton, 2004). Additional processes, e.g. shifts in attention and common associations may add to the phenomenon and underlie response enhancement in other reinstatement designs (e.g. when extinction and reinstatement context are identical but both different from the test context (Westbrook et al., 2002) .

As it is beyond the scope of this manuscript to give a comprehensive picture of the past 40 years of rodent work on the reinstatement phenomenon and the different theoretical explanations, we refer the interested reader to other excellent and important sources (Bouton, 2004; Rescorla, 1979; Westbrook, Iordanova, McNally, Richardson, & Harris, 2002).

While these systematic investigations reveal the important role of the context in reinstatement in rodents, the importance of contextual influences in humans has been shown as well, albeit mechanistic explanations and comprehensive studies are missing.

2. **Reinstatement in humans**

2.1 Type of conditioning protocol and generalized vs. differential reinstatement effects

In humans, reinstatement effects have been observed in single-cue studies (LaBar & Phelps, 2005 [Exp.1]; Schiller et al., 2008) mirroring experimental protocols and results of rodent work (Frohardt et al., 2000; Harris, Jones, Bailey, & Westbrook, 2000; Laurent & Westbrook, 2010; Morris, Westbrook, & Killcross, 2005; Westbrook, Iordanova, McNally, Richardson, & Harris, 2002b). The majority of human studies has, however, used differential protocols. In differential conditioning, typically one of two initially neutral stimuli is paired with the US during acquisition, while the other one (CS-) is not. Differential protocols allow for within-subject comparisons of the US-associative memory and can thus control for the effects of orienting responses and sensitization effects (as these processes would affect CS+ and CS- in

a similar vein) and allow for testing of generalization effects. In contrast, only one rodent study used a differential conditioned suppression protocol in mice demonstrating *differential* (that is, CS+-specific) ROF in the reinstatement but not in the no-reinstatement US control group (Dirikx, Beckers, et al., 2007).

In humans the picture is complex: Differential protocols yielded evidence for reinstatement specifically to the CS+, but not to the CS- (*differential reinstatement*). While some of the studies also observed, to a certain degree, enhanced responding to the CS- despite of a more pronounced enhancement for the CS+ (Dirikx, Hermans, Vansteenwegen, Baeyens, & Eelen, 2007; Kull, Müller, Blechert, Wilhelm, & Michael, 2012; Milad, Orr, Pitman, & Rauch, 2005), other studies demonstrate ROF to both CS+ and CS- to the same degree (*generalized reinstatement*). Whether ROF is specific for the CS+ or generalized to the CS-(s) is important, since the ability to discriminate safety cues from threat cues is negatively associated with pathological anxiety (Lissek et al., 2005) and predictive of resilient responding to life stress (Craske et al., 2012) (see also *4.1*). Furthermore, it's not the mere enhancement of responses (observed in both, differential and generalized reinstatement), but the ability to maintain a discrimination under aversive circumstances which might critically underlie long-term remission and/or resilience.

Interestingly, the observation of non-differential (generalized) ROF is also evident in other ROF phenomena such as renewal (reviewed by Vervliet et al., 2013a) and spontaneous recovery (Norrholm et al., 2008). Further complicating matters, often a mixture of differential, generalized and no reinstatement effects in different dependent measures is reported within one study (see **Table1** for a detailed summary of the results of human studies). The high frequency of non-differentially enhanced responding following reinstatement may question whether genuine association-based processes (e.g. stimulus generalization due to stimulus similarity) or rather sensitization or orienting effects to uncertainty are underlying mechanisms and these need to be controlled for using an adequate

study design (see recommendations for future studies, Table 4). As discussed in the framework of renewal studies (Vervliet, Baeyens, et al., 2013), generalized ROF does however not preclude genuine association-based effects to the CS+ but may result from associative learning to the CS- as well. Inclusion of additional control stimuli that are present only during the acquisition of fear and the reinstatement test (i.e.. not extinguished stimulus) or only during reinstatement test (e.g. novel stimulus) may be used to control enhancement of responses due to association between the stimulus and the context and thus prove useful in future studies.

Inclusion of a control group that did not receive any reinstatement-USs also allows controlling for effects that are due to the experimental break between extinction and reinstatement test (e.g. sensitization or orienting responses and/or return of fear phenomena as renewal or spontaneous recovery) (see recommendations for future studies, **Table 4**) and the importance of control groups becomes evident from the fact that in some human studies, enhanced reactions are not only observed in the experimental but also the no reinstatement-control group (see **Table 1, Figure 1**) (Dirikx, Hermans, et al., 2007; Dirikx, Vansteenwegen, Eelen, & Hermans, 2009; Hermans et al., 2005; Kull et al., 2012 two unpublished data-sets (Dirikx, T., 2006).

-- Insert Table 1 about here --

2.2. Dependent measurements

In human studies, CRs are commonly indexed by skin conductance responses (SCRs) or levels (SCL), fear potentiated startle (FPS), fear and US expectancy ratings (ratings) or reaction time tasks (RT) (see **Table 3**). Only recently, studies using fMRI have emerged (Kattoor, Gizewski, et al., 2013; Kattoor, Thürling, et al., 2013; Lonsdorf, Haaker, Fadai, & Kalisch, 2013; Lonsdorf, Haaker, & Kalisch, 2014). It is obvious from an overview of the

results in these different measurement modalities (see **Table 1 and Figure 1**), that the type of dependent measurement does not explain the occurrence of differential vs. generalized reinstatement vs. non-significant reinstatement. This suggests that different dependent measures do not seem to be differently susceptible to the reinstatement effect as the proportion of differential vs. generalized effects is similar for all measures. From Figure 1, it seems as if reinstatement effects in the control group (no reinstatement US group) is mainly observed in non-physiological measures (ratings, RT), but it has to be noted, that only few studies have employed control groups (see Table 3 for details) and only three of these (Kull et al., 2012; Norrholm et al., 2006; Sokol & Lovibond, 2012) have recorded psychophysiological parameters (FPS, SCL or SCR).

Individual studies have mainly relied on single psychophysiological measures and few studies have acquired multiple psychophysiological measures (Haaker, Lonsdorf, Thanellou, & Kalisch, 2013; Kindt & Soeter, 2013; Sevenster, Beckers, & Kindt, 2012a). As different psychophysiological measures are thought to tap different processes, comparability between the results of different studies is not straightforward. SCRs for example reflect contingency awareness while FPS is thought to be more fear-specific (e.g. Weike, Schupp, & Hamm, 2007). To promote comparability between studies, future work should focus on multimodal assessments and report reinstatement effects in all measures acquired. In addition, calculation of reinstatement effects in measurements of baseline or contextual anxiety is needed to draw conclusions of the specificity underlying the ROF as well as to investigate sensitization effects, e.g. assessment of ITI startle or baseline startle measurement.

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2.3 Calculation of reinstatement effects

Due to the fact that the reinstatement effect in humans does not last over many non-reinforced test trials, the exact way of statistically quantifying it is important. Statistical calculations vary widely in between- and within- laboratories (see **Table 3**) and some recommendations would certainly aid the field in promoting comparability between studies and reducing arbitrary testing (see also recommendations for future studies, **Table 4**). While some authors have conducted single-trial analyses others have used blocks of 2 to 6 trials for statistics (see **Table 3**). As single trial data, and in particular psychophysiological measures, tend to be rather noisy, they might be more prone to suffer from low reliability whereas small blocks of trials (e.g. 2-3 trials/CS type) may better capture the expected reinstatement induced response enhancement and yield more robust information. On the down-side, trial blocks may include trials that reflect an already faded or extinguished phenomenon and thus might underestimate the effect. In any case, single-trial graphs should be presented to allow for an evaluation of the duration and differentiality of the effects.

Most studies have performed the crucial statistical test for reinstatement effects comparing CRs occurring immediately before to CRs immediately following reinstatement USs in a 2 (time) x 2 (CS type) ANOVA (see **Table 3** "factor time in RI"). Some studies have performed statistical analyses separately for CS types (CS+/CS-) or the experimental and the no reinstatement-US control group (if included). While this provides important *additional* information, the critical test is a *direct* statistical comparison of responses to both CS types and time-points (prior to vs. post-reinstatement) as well as between groups (if applicable). This is, a significant difference between both time-points (main effect of time) may indicate a generalized reinstatement of responses and CS-type specific changes (CS x time interaction) after reinstatement may imply a differential enhancement of responses. However, this interaction in an analysis comprising of both CS types and time-points denotes a differential reinstatement that cannot be inferred by separate testing of CS-types or time-points.

The factor time (prior to vs. post-reinstatement) requires an additional note: In single-day studies, reinstatement follows immediately upon an extinction or a second extinction (re-extinction) phase allowing for a direct comparison between CSs elicited immediately before and after the reinstatement manipulation. Using a delayed reinstatement test occurring on a different day than acquisition and extinction also warrants caution. When no other test trials (see above) precedes reinstatement US administration on the same day (as in e.g. Schiller et al., 2008, 2010) an unequivocal attribution of response enhancement to reinstatement processes is not possible. In this scenario, initial reactivity, orienting responses and spontaneous recovery effects likely also contribute to response enhancement.

Furthermore, the crucial test for reinstatement (time x CS type ANOVA) can be extended to a time x CS type x group (reinstatement vs. control group) ANOVA, which provides the most reliable information about genuine reinstatement effects. To date, only one third of the human studies have used a no-reinstatement US control group and some of these even report significant response enhancement in the control group that did not receive unsignalled USs. This highlights the importance of the necessity to control for non-specific effects and more work is needed to understand the processes underlying this non-specific response enhancement in no-reinstatement-US control groups.

In sum, genuine reinstatement effects have to be quantified by a repeated measures analysis involving time, CS-type and possibly group (reinstatement vs. control group). A main effect of time (where post reinstatement > prior to reinstatement) can be interpreted as a generalized reinstatement effect, while a time x CS type interaction would be required for differential reinstatement. If both tests turn out to be significant, a generalized reinstatement that might be most pronounced for one CS type can be concluded. In addition, care needs to be taken to employ a (re-extinction) phase before reinstatement in order to be able to disentangle genuine reinstatement effects from spontaneous recovery effects. We also refer to Table 4 where a list of methodological and design recommendations for future studies is collected. In the

following we have compiled a summary of possible experimental as well as biological and trait markers that may affect the reinstatement phenomenon in humans.

3. Possible experimental boundary conditions in human reinstatement studies

3. 1. Spatial manipulation of reinstatement context

Despite the extensively studied contextual influences on reinstatement in rodents (see above), only two human single-cue studies compared reinstatement between participants receiving reinstatement USs in the same ($A_{acq.}A_{ext.}\mathbf{A}_{reinst.}A_{reinst.test.}$) or a different (AA**B**A) room ("*spatial reinstatement context*") in which any testing took place (LaBar & Phelps, 2005; Schiller et al., 2008) (see **Table 2**). Participants undergoing no spatial contextual change (AA**A**A) showed pronounced and significant reinstatement in both studies, while the AA**B**A group exhibited no reinstatement effects (LaBar & Phelps, 2005) or less pronounced response enhancement (Schiller et al., 2008; likely due to the intermixture with spontaneous recovery effects). These results nicely mirror early rodent findings (Bouton & Bolles, 1979) and highlight the role of the context also in humans. However, the role of the context in humans has not been explored further in detail and largely been neglected in later studies (see also ***3.2***). Recently we followed up on the role of the context in reinstatement by using cued as well as contextual conditioning in a within-subject design. In this design, the CSs are embedded in the context, which are a picture of a room (as done in e.g. Fonteyne, Vervliet, Hermans, Baeyens, & Vansteenwegen, 2010; Marschner, Kalisch, Vervliet, Vansteenwegen, & Büchel, 2008). Previous studies have used this distinction of a discrete symbol (as a CS) and the surrounding environmental stimuli (as a context) to study contextual influence on fear conditioning in humans, as well (Kalisch et al., 2006; Milad et al., 2005; Milad et al., 2007). CSs were predictably followed by the US, whereas the time-point of the US administration to the context was unpredictable. Importantly, neither the CS nor the conditioned context was present during the administration of the reinstatement USs. We demonstrated more

pronounced reinstatement effects towards the conditioned context as compared to the CSs using psychophysiological measures (Haaker, Lonsdorf, et al., 2013) and fMRI (Lonsdorf et al., 2014), further adding evidence for the role of context conditioning in reinstatement. This is of importance, as human research focused exclusively on reinstatement to CSs (e.g. symbols depicted on the computer screen). Future studies in humans are needed to bridge this gap and investigate contextual boundary conditions of reinstatement in detail. However, the attenuation of the responses to the CSs may as well be a result of the presence of the conditioned context, which are a better predictor of the US after reinstatement (because reinstatement US are not CS predicted US, see below). This would be supported by the observation of Rescorla and Cunningham (1977, Exp. 2) that the presence of a stronger predictor for the US (e.g. unextinguished CS) during reinstatement test attenuates the ROF of another CS (test-CS). Of note, both CSs were unreinforced during reinstatement test.

3.2. Visual stimulation during reinstatement US administration

One feature of the spatial reinstatement context is the visual input during reinstatement US administration ("*the visual reinstatement context*"). In contrast to studies in rodents, where a context is defined as the whole box in which the animal is placed, stimuli in human studies are presented on computer screens. However the role of the visual stimulation on that screen during reinstatement has so far been neglected and consequently there is large variety between studies, which may partly explain divergent findings. Studies have used the inter-trial interval (ITI) background, the cue background (i.e. what is on the screen during CS presentation) or a neutral background (i.e. screen that has not been presented in the experiment before) as visual reinstatement context and many studies do not report what was shown (see **Table 3**). It can be supposed, that a new association between the visual reinstatement context and the reinstatement USs might be formed which may imbue the visual

context with a sense of danger. Consequently, it should have an impact on the results at test, if the ITI or the cue background is reinforced, which may be due to different associations between the CS and both contexts: The cue background is presented simultaneously with the CS during all experimental phases (except the reinstatement), whereas the CS is always absent during ITI presentation.

In addition, it needs to be considered that any change in the visual background context may evoke effects related to contextual change (e.g. renewal) and that the presentation of any conditioned context or CS during reinstatement may also induce additional processes e.g. re-acquisition. That is, if a former CS, which has already been extinguished, is presented during reinstatement US presentation, this may lead to new (or reacquired) fear conditioning towards this CS.

Furthermore, beyond visual and spatial context definitions, also temporal, interoceptive, cognitive or social features contribute to associative contextual characteristics (Bouton 2004; Maren et al. 2013) and most of these remain unexplored to date.

Beyond these, the visual input may also trigger non-associative cognitive processes, which might exert an impact on reinstatement effects. The reinstatement context might become aversive through the generation of uncertainty by an obvious or sensed experimental break. This contextual change may be related to subtle, but critical details in experimental design of human studies (e.g. physical reinstatement context, visual reinstatement context, subjective ratings) and might explain the enhancement of CRs in human control groups without any US presentation (see also **Table 1**). If these subtle changes in context contribute to reinstatement, reinstatement might, in part, be considered as a special case of renewal.

Furthermore, the reinstatement procedure (i.e. USs that are not predicted by a CS) may induce uncertainty/unpredictability in humans by challenging the previously learned associations, that is, the CS+ during reinstatement is not reliably predicting the (reinstatement) US. Experiments of Rescorla & Cunningham (1977) could show that if the reinstatement USs are

signalled by a CS (re-aquisition-CS i.e. not reinstatement but reacquisition), the presence of this re-aquisition-CS during reinstatement test attenuates reinstatement to another CS (test-CS, not present during the reinstatement USs). However, if only the test-CS is present, reinstatement will occur, despite of the "signalled reinstatement", i.e. reacquisition. These findings can be interpreted in terms of uncertainty in humans, namely that ROF during reinstatement is abolished by the presence of a good predictor of the US that reduces uncertainty of US contingencies.

This uncertainty about the predictive value of the CS may be derived from contextual conditioning during reinstatement: The context gains associative value through the unexpected presentation of the USs (Pearce & Hall, 1980), which possibly shifts the balance of attention from a focus on the CS towards the context (Schmajuk et al., 2007) and enhances contextual anticipatory anxiety (Grillon, Baas, Cornwell, & Johnson, 2006). Upon subsequent CS-reoccurrence, the discrimination of the previously US-predictive CS+ and non-predictive (safe) CS- might be challenged, as their predictive value for the US is attenuated as compared to the enhanced US predictive value of the context. Supporting this idea, we found that reinstatement increases anticipatory anxiety, as indicated by response enhancement during the ITI (Haaker et al., 2013) as well as reactivity towards the conditioned context as compared to the CSs (Haaker et al., 2013; Lonsdorf et al., 2014, see above).

In a translational perspective, Grupe and Nitschke (2013) described uncertainty as a key factor for clinically relevant anxious behaviour. According to their model, uncertainty leads to the persistence of previously learned responses and decreases the ability to inhibit defensive responses towards safety signals. This might explain a reduced discrimination of the CS+ and the CS- following reinstatement, which is reflected in the high frequency of generalized reinstatement in humans.

3.3. Experimental timing

In rodent studies have demonstrated that timing of reinstatement US presentation with respect to reinstatement context onset has an impact on the degree of reinstatement (Richardson, Duffield, Bailey, & Westbrook, 1999), an experimental detail which has not been given attention in human work. Furthermore experimental phases (acquisition, extinction, reinstatement, reinstatement test) usually take place on distinct days while in human studies they often follow upon each other immediately (see **Table 2**), which hampers translation between species. Furthermore, there is increasing evidence that experimental timing has an impact on ROF in humans (e.g. Golkar & Öhman, 2012; Huff, Hernandez, Blanding, & LaBar, 2009) and animals (Myers, Ressler, & Davis, 2006; but see Schiller et al., 2008; Woods & Bouton, 2008) and may rely on different molecular mechanisms (Cain, Godsil, Jami, & Barad, 2005). Separating conditioning and extinction learning in time allows for memory consolidation and thus represents a more naturalistic model for clinical relapse as usually time elapses between a traumatic event, CBT and relapse.

Still, few reinstatement studies have separated experimental phases (acquisition - extinction, extinction - reinstatement US administration, reinstatement US administration - reinstatement test) in time: In most cases, reinstatement (both reinstatement US administration and test) was tested immediately following extinction, which was 24 hours delayed or immediately followed upon acquisition. Reinstatement after 24h delayed extinction (Golkar & Öhman, 2012; Norrholm et al., 2006; Sevenster et al., 2012a [uninstructed extinction group]) was more pronounced as compared to reinstatement following immediate extinction (un-masked stimuli; Golkar & Öhman, 2012). Others (Milad et al., 2005; Schiller et al., 2008) have separated reinstatement testing (preceded by the reinstatement US on the same day) 24h after extinction learning, but both studies used immediate extinction after acquisition in the first place. In addition, the results of both studies are not unequivocally attributable to reinstatement effects as the reinstatement test followed immediately upon a recall as well as a

renewal test in one study (Milad et al., 2005), and it was intermixed with spontaneous recovery and orienting responses in the other study as no extinction or a second extinction (re-extinction) phase immediately preceded reinstatement (Schiller et al., 2008). The use of no-reinstatement US control groups in these studies would have enhanced interpretability of these data.

Recently, there seems to be a trend towards separating acquisition, extinction, extinction recall/re-extinction and reinstatement in time (Haaker et al., 2013; Kindt & Soeter, 2013; Lonsdorf et al., 2014), and there is preliminary evidence that reinstatement might occur even after a long time delay of one month (Kindt, Soeter, & Vervliet, 2009) or one year (Schiller et al., 2010) after re-activation/re-consolidation and successful extinction. However these tests do not represent pure reinstatement effects as these were contaminated by the drug vs. placebo manipulations (Kindt et al., 2009) and an intermixture of reinstatement effects with spontaneous recovery (Schiller et al., 2010) may bias the results.

In addition, timing within the phase of reinstatement US administration varies widely (see **Table 3**). That is, for instance, the time gap from the last reinstatement US administration to the first test trial, the occurrence of ratings or other tasks (e.g. RT tasks, reminder CSs) before the first reinstatement test trial. In particular ratings or brakes may be perceived as indicator of contextual change and induce uncertainty (Pineño & Miller, 2004). Most problematic, these experimental details are often reported only rudimentary which hampers an evaluation of their influence.

Future studies should report this information in detail and consider the impact of experimental timing. In particular, to provide a plain measure of reinstatement, extinction/re-extinction should be employed before the reinstatement manipulation to separate genuine reinstatement processes from spontaneous recovery and orienting. Further, caution is warranted in multiple day paradigms that use multiple US calibrations as this procure may function in itself as reinstatement.

3.4. Reinstatement induces only very transient effects in healthy participants

While a differential rodent study has shown very slow extinction of the reinstatement effect (Dirikx, Beckers, et al., 2007), the response enhancement in humans seems to be very transient and manifests as on average one to three single enhanced responses following reinstatement USs administration in FPS (Gazendam & Kindt, 2012; Kindt & Soeter, 2013; Sevenster et al., 2012a), SCL (Milad et al., 2005), SCRs (Kindt & Soeter, 2013) and up to four single enhanced trials in US expectancy ratings (Gazendam & Kindt, 2012; Golkar & Öhman, 2012 ; Kindt & Soeter, 2013; Norrholm et al., 2006; Sevenster et al., 2012a (normal extinction > instructed extinction)). To date, a single human study showed statistically that reinstatement effects in fear and US-expectancy ratings did not survive 16 un-reinforced CS+ and CS- presentations (Hermans et al., 2005). As returning CRs are typically only evident in a few trials, reinstatement effects might be particularly susceptible to stimulus sequence effects. For instance, it is likely that, if the first CS after reinstatement is an unreinforced CS+, some participants may expect a US to the CS-, which may in part explain non-differential ROF in comparison to sequences were the first trial is an unreinforced CS-. This may be particularly pronounced in paradigms using a 100% reinforcement ratio. Therefore, stimulus sequences following reinstatement need to be carefully balanced and reported in detail.

While in healthy populations the reinstatement effect is very transient (i.e. lasts only for a limited number of test trials), studies of fear learning and reinstatement with ecologically valid USs in patient populations are eagerly awaited. Until then, it can only be hypothesized that reinstatement effects in patients might be more stable over time and of different quality (e.g. more generalized). Furthermore, in patients a very brief induction of fear might be sufficient induce full blown clinical relapse and avoidance behaviour.

3.5. Number of extinction trials/ Amount of extinction success

According to Bouton (Bouton, 2004), ROF represents the re-occurrence of the CR to an extinguished CS, most likely due to an underlying association of the CS with the US. Thus, a crucial determinant of the degree of ROF following reinstatement might be the strength of the corresponding CS-US association (fear memory) as opposed to the inhibitory CS-no US association (extinction memory). The balance of one over the other might be affected by the number of conditioning and/or extinction trials as well as their relative proportion. In support of this, rodent work on renewal suggests that massive extinction learning attenuates renewal effects as compared to moderate extinction (Denniston, Chang, & Miller, 2003).

It is important to note, that some studies have excluded "non-extinguishers" or included additional extinction trials for non-extinguishers (see **Table 3**) to achieve comparable end-point extinction performance or, in other words, associative memory strength. The impact of this has however not yet been investigated. We performed an exploratory comparison of studies showing differential or generalized reinstatement in different dependent measures with respect to the trial-numbers in conditioning and extinction[1]. This suggested that a higher number of extinction, but not conditioning trials, was overrepresented in studies reporting differential reinstatement. However, a study statistically comparing the role of different numbers of extinction trials as well as different CS durations during extinction (Golkar, Bellander, & Öhman, 2013) found no impact of the amount of extinction on the degree of the reinstated FPS. In addition the reduction of fear as well as the fear level at the end of a therapy was found to have no impact on therapeutic outcome (Craske et al., 2008).

Future studies should address how the degree of fear acquisition and extinction learning influences the reinstatement of fear. Additionally, the proportion of ROF related to the expression of fear memory at the outset of extinction may offer a supplementary index of reinstatement. As resistance to reinstatement might be interpreted as an indicator of a pre-dominant extinction memory trace, studies focusing on this might provide important clues for

the enduring endeavour in finding ways to strengthen extinction memories and enhance CBT efficacy.

3.6. Type of CS and US stimulation

Studies have used neutral pictures such as geometrical shapes, neutral faces, colored lights as well as fear-relevant pictures (fearful/angry faces, spiders) as CSs (see **Table 2**). Studies have so far almost exclusively focused on discrete CSs and only two studies (Haaker, Lonsdorf, et al., 2013; Lonsdorf et al., 2014) investigated reinstatement to CS (geometric shapes) and conditioned contexts (pictures of rooms on which the geometric shapes were superimposed) in a within-subject design. As described above, the context seemed to be more affected by the reinstatement as compared to the CSs in two independent samples.

While the type of CS varies widely, the most commonly used US-type in human fear conditioning and reinstatement is electro-tactile stimulation, but also a loud tone, an air blast to the throat or visceral pain has been employed (see **Table 2)**. USs types differ in their inherent aversiveness (Glenn, Lieberman, & Hajcak, 2012; Sokol & Lovibond, 2012) and the choice of US type might be critical as only CRs to an conditioned predictor of an electrotactile US, but not to a human scream, were found to be correlated with trait anxiety (Glenn et al., 2012).

The majority of the studies used 100% reinforcement (min 66.6% ; see **Table 2**) and there does not seem to be a relationship between different reinforcement ratios and the outcome of reinstatement. Also, in human studies, nearly all have used identical US types during fear acquisition and reinstatement. Of note, reinstatement has also been observed after presenting a different US type during reinstatement ($US_{reinst.}$) as compared to fear acquisition ($US_{acq.}$) in rodents (different intensity: Kim & Richardson, 2007; qualitatively different: Rescorla & Heth, 1975) and humans (noise and electrotactile: Sokol & Lovibond, 2012). Of note, human participants expected occurrence of the $US_{reinst.}$ and not the $US_{acq.}$ during test following the

reinstatement manipulation (Sokol & Lovibond, 2012). This demonstrates that other aversive experiences than the $US_{acq.}$ are capable of mediating ROF. As aversive or stressful life events affect relapse risk in anxiety related disorders (Wade, Monroe, & Michelson, 1993) this might be of particular clinical relevance. In support of this, a recent rodent study showed that the presentation of an unextinguished CS+ (predictive of the US during acquisition) can reinstate the CR to an extinguished CS+ (Halladay, Zelikowsky, Blair, & Fanselow, 2012). Earlier series of experiments (e.g. Rescorla & Heth, 1975 exp 2) have observed this induction of reinstatement as well, albeit they did not observe strong evidence for this manipulation as compared to reinstatement through US presentation.

This induction of reinstatement may be related to the aforementioned observation of *mediated conditioning* in ROF (see above), meaning that reinstatement may be due to an common association of the extinguished CS and the US, as well as between the US and the unextinguished CS+ (used to reinstate the CR).

In conclusion, reinstatement does not necessarily increase the expectation of the $USs_{acq.}$ And the observation of ROF following a different aversive event than the actually feared event dramatically enhances the chances for ROF in every-day life.

3.7. Instruction vs. non-instruction

Of note, the majority of reinstatement studies used instructed acquisition (see **Table 2**), mostly providing explicit information that "one stimulus will always/sometimes be followed by the US" while fewer studies told participants "to look for contingencies between the stimuli and the US". As instructed and uninstructed conditioning might tap different processes, this may be translate into different behavioural and neural correlates (Maier et al., 2012; Mechias, Etkin, & Kalisch, 2010).

The extinction learning phase in turn has mostly been uninstructed, likely because it immediately has followed upon the acquisition phase (see **Table 2**) and in few cases

participants were told “to remember what they had learned during acquisition” or that they “might be or not be” shocked. A direct comparison of reinstatement effects following instructed acquisition and 24h-delayed instructed or uninstructed extinction (Sevenster et al., 2012a) found reinstatement in FPS in both the instructed and the non-instructed extinction group. In SCRs and US expectancy ratings responding was however completely abolished during instructed extinction and did not return after reinstatement. In addition, reinstatement of SCRs was also attenuated during another type of social learning, namely observational extinction (e.g. after regular fear conditioning, participants observed a confederate undergoing extinction) as compared to direct extinction (Golkar, Selbing, Flygare, Ohman, & Olsson, 2013). While instructed and observational extinction might attenuate ROF, explicit tests of the effect of instructed vs. un-instructed acquisition are still awaited. In addition, new data from our group show, that reinstatement, assessed by SCRs, FPS, fear and US expectancy ratings is equally pronounced to a CS that was actually predictive of the US and to a CS that was said to be predictive of the US, whereas it in fact was never followed by the US during acquisition (Mertens, Kuhn et al., in preparation).

4. Individual and biological differences

In addition to experimental boundary conditions, individual differences may be related to the observation of generalized or differential reinstatement effects. In addition pharmacological manipulations affecting ROF a well as the neural correlates have just begun to be studied.

3.1. Self reported anxiety

Different studies from Merel Kindt’s lab suggest that reinstatement of the CS- responses is correlated with trait anxiety (Kindt et al., 2009 [in FPS in a propranolol-no reactivation group only]; Kindt & Soeter, 2013 [in SCR]; Soeter & Kindt, 2010 [in SCR in the placebo group only]). Interestingly, in the Kindt et al. (2009) study, the only experimental group showing

this correlation was characterized by significantly higher trait anxiety scores than the other experimental groups. In addition, they have shown that accounting for trait anxiety as a covariant in the reinstatement analysis (SCRs) changed results from generalized to differential reinstatement effects (Kindt & Soeter, 2013). Our own data (unpublished findings) support these preliminary findings in showing that a CS+/CS- discrimination index after reinstatement correlates negatively with state anxiety, which is driven by enhanced CS- responses in the high state anxiety group and by a CS+-specific increase in the low state anxiety group.

Vervliet (Vervliet, Craske, & Hermans, 2013) suggests two mechanistic explanations for this observation: anxious individuals may be prone to generalization (Lissek u. a., 2009; Shmuel Lissek u. a., 2010) and/or exhibit profound contextual anxiety (Grillon, 2002). In addition, high anxious individuals might be more prone to the perception of uncertainty after reinstatement, which might be reflected in the disinhibition of the CR to signals of safety. Beyond individual traits, the experimental induction of worrying by presenting catastrophic questions regarding the participants' tolerance for the US between acquisition and immediate extinction impaired extinction and thus also enhanced ROF after reinstatement as assessed by US expectancy ratings but not FPS (Gazendam & Kindt, 2012).

In sum, anxious individuals might be more prone to display stronger and less differential reinstatement, a picture that presents similarly for other return of fear phenomena (for a review Boschen, Neumann, & Waters, 2009). Furthermore, as noted above, the choice of US type might also be critical as only the CR to an electrotactile, but not to a scream US, was correlated with trait anxiety during fear learning(Glenn, Lieberman, & Hajcak, 2012).

3.2. Awareness

Some reinstatement studies provide information about participants CS/US contingency awareness following acquisition and most of these studies have excluded unaware participants (see **Table 3**). Exclusion was based on post-experimental interviews or non-differential SCRs

during acquisition (taken to indicate lack of conditioning success). In particular the latter might affect whether response enhancement following reinstatement is generalized or differential as participants exhibiting less differential responding during acquisition might also show less differential reinstatement. The effect of excluding or including unaware participants has however not been systematically studied to date with respect to reinstatement. A single study has experimentally manipulated awareness of the CSs during extinction learning through backward-masking and observed differential reinstatement in FPS (compare experimental timing section)(Golkar & Öhman, 2012).

3.3. Reconsolidation

Reconsolidation is a process whereby previously consolidated memories can be reactivated and again rendered sensitive to disruption (e.g. Nader, Schafe, & Le Doux, 2000). Extinction training within the reconsolidation time-window following reactivation was found to abolish reinstatement [though intermixed with spontaneous recovery, see above (Schiller et al., 2010)]. However, reinstatement was observed in different follow up studies that tried to replicate these findings using FPS, SCR and US-expectancy ratings (Soeter & Kindt, 2011[exp.2])(Golkar, Bellander, Olsson, & Ohman, 2012)(Kindt & Soeter, 2013). Reinstatement, similar to reactivation, induces retrieval of the CS-US memory trace. Instead of using a single CS reactivation trial, using a single US reactivation trial might also render the CS-US associative memory labile and sensitive to disruption (see Lonsdorf et al., 2013 for a discussion). To date this is highly speculative and to our knowledge, this hypothesis has not been tested explicitly in rodents or humans and it would be interesting, if protein-synthesis inhibition following reinstatement US administration would disrupt the context – US association that is thought to mediate the reinstatement effect. This relates to the report by Debic and colleagues (Deębiec, Doyère, Nader, & LeDoux, 2006) who showed that directly reactivated memories become labile and consequently their consolidation becomes

susceptible to protein synthesis inhibition while indirectly reactivated (i.e., associated through 2nd order conditioning) memories do not.

4.4. Pharmacological manipulations

In rodents, reinstatement can occur after biological manipulations such as systemic epinephrine (Morris et al., 2005) or adrenocorticotropin administration (Richardson, Riccio, & Devine, 1984) as well as arousal-triggering electrical stimulation of the amygdala (Kellett & Kokkinidis, 2004). In humans, some biological candidate systems have been investigated namely the adrenergic system and the endogenous cannabinoid system. Antagonism of beta-adrenerig receptors (using Propranolol) 24 hours after conditioning (and 24hours before extinction) does not attenuate response enhancement after reinstatement (Kindt et al., 2009). However, responses are not enhanced when a CS reactivation trial precedes the noradrenerigc manipulations described above (Kindt et al., 2009; Soeter & Kindt, 2011[exp.1]) or if the reactivation violates the expected US occurrence (e.g. prediction error) (Sevenster, Beckers, & Kindt, 2012b) (Sevenster, Beckers, & Kindt, 2013).

Noradrenaline reuptake inhibition (though Reboxetine) directly after extinction did not affect reinstatement one week later in psychophysiological measurements but seemed to lead to activation of the fear network in fMRI (Lonsdorf et al., 2013). Administration of Cannabidiol, which increases levels of the endogenous cannbinoid anandamide prior and post extinction learning reduced differential SCRs to CSsafter reinstatement (Leweke et al., 2012) and decreased US expectancy to the CSs as well as their surrounding context after reinstatement when given only after extinction learning (Das et al., 2013). Dopaminergic enhancement after extinction learning was found to reduce reinstatement of conditioned contexts in humans (Haaker, Lonsdorf, Fadai & Kalisch in preparation) as well as in mice (Haaker, Gaburro, et al., 2013). These data suggest that also in humans biological

manipulations have an impact on reinstatement but the exact underlying pathways remain unstudied.

4.5. Neural correlates of reinstatement

Studies of the neural system mediating reinstatement in rodents observed a critical role of the amygdala and hippocampus for the ROF through reinstatement (Frohardt, Guarraci, & Bouton, 2000; amygdala: Laurent & Westbrook, 2010; hippocampus: Wilson, Brooks, & Bouton, 1995). In particular, as both regions have been implicated in the processing of contextual stimuli and other ROF phenomena in rodents (Maren et al., 2013; Maren, 2011; Quirk & Mueller, 2008) these findings line up with the important role of the context in reinstatement (see above).

The first study addressing the neural underpinnings of reinstatement in humans found reinstatement to be abolished in patients with hippocampus lesions (LaBar & Phelps, 2005). Only recently, studies emerged that investigated the neural network underlying reinstatement effects using functional imaging. Two studies using a visceral pain US and a cue-conditioning paradigm found trend-wise differential (CS+>CS-) hemodynamic responses *after* reinstatement in the parahippocampus (Kattoor, Gizewski, et al., 2013) and the cerebellum (Kattoor, Thürling, et al., 2013). An additional study using cued and contextual conditioniong found significant and widespread (anterior) hippocampus activation to the contexts in the critical reinstatement test (after>before reinstatement) in two independent samples (Lonsdorf et al., 2014). Furthermore, significant differential responses to the conditioned contexts were observed in the amygdala and the dmPFC after reinstatement mirroring previous animal work and once again highlights the role of the context-responsivity in reinstatement. Enhanced responses to the cued stimuli in turn were observed in the subgenual ACC/vmPFC, an area commonly implicated in fear inhibitory and regulatory processes (Lonsdorf et al., 2014), which might be an epi-phenomenon of the combined context and cue conditioning design.

5. Summary and future perspectives

From this overview, it becomes clear that research on the reinstatement phenomenon in humans is still in its infancy. In this review, we have provided a detailed overview for the existing human studies (see also Tables 1-3) and compiled a number of possible experimental boundary conditions that we believe may impact on the degree of ROF following reinstatement.

There is a large variety with respect to experimental design, data analysis and consequently results are currently difficult to interpret and put into context. To foster fruitful future research and raise awareness with respect to some critical methodological considerations, Table 4 is meant as a guide for future studies. Table 4 lists the major recommendations given throughout the review, both with respect to study design and data analysis.

To round our review off, the probably most puzzling and unanswered questions in human reinstatement research is what factors contribute to generalized, differential or absent reinstatement effects or even reinstatement in no-reinstatement US control groups and how this relates to clinical populations. The experimental boundary conditions, state, trait or biological factors that may contribute to these different observations in humans have not yet been *systematically* evaluated and it cannot be excluded that multiple mechanisms may interact to determine the degree and quality of reinstatement.

Currently, we do not know under which conditions reinstatement in humans occurs and whether theories derived from rodent work are also able to explain all results in human differential conditioning protocols or whether additional mechanisms (e.g. cognitive processes like expectancy and uncertainty) might play a major role in humans. Finding answers to these questions is of high priority given that reinstatement in humans has recently been established as the major outcome measure for conditioning and extinction memory consolidation manipulations in humans.

Despite of these remaining questions, rodent and human work show quite some parallels (e.g. the role of the context) and more in-depth experimental work in humans and translation to clinical populations is needed, as the prevention of relapse is an important topic from both a scientific and a social point of view. We are at a point, where we know ways to reduce fear, but the current challenge is, how to maintain remission and prevent relapse.

Footnotes

[1] We collapsed different types of dependent measurements used in each study and compared the trial number between the reports of differential and generalized reinstatement,

REFERENCES

Boschen, M. J., Neumann, D. L., & Waters, A. M. (2009). Relapse of successfully treated anxiety and fear: theoretical issues and recommendations for clinical practice. *Australian and New Zealand Journal of Psychiatry*, *43*(2), 89–100. doi:10.1080/00048670802607154

Bouton, M. E. (1984). Differential control by context in the inflation and reinstatement paradigms. *Journal of Experimental Psychology: Animal Behavior Processes*, *10*(1), 56–74. doi:10.1037//0097-7403.10.1.56

Bouton, M. E. (2004). Context and behavioral processes in extinction. *Learn.Mem.*, *11*(5), 485–494.

Bouton, M. E. (2004a). Context and behavioral processes in extinction. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *11*(5), 485–494. doi:10.1101/lm.78804

Bouton, M. E. (2004b). Context and behavioral processes in extinction. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *11*(5), 485–494. doi:10.1101/lm.78804

Bouton, M. E., & Bolles, R. C. (1979a). Role of conditioned contextual stimuli in reinstatement of extinguished fear. *Journal of Experimental Psychology. Animal Behavior Processes*, *5*(4), 368–378.

Bouton, M. E., & Bolles, R. C. (1979b). Role of conditioned contextual stimuli in reinstatement of extinguished fear. *Journal of Experimental Psychology. Animal Behavior Processes*, *5*(4), 368–378.

Bouton, M. E., & King, D. A. (1983). Contextual control of the extinction of conditioned fear: tests for the associative value of the context. *Journal of Experimental Psychology. Animal Behavior Processes*, *9*(3), 248–265.

Bouton, M. E., & King, D. A. (1986). Effect of context on performance to conditioned stimuli with mixed histories of reinforcement and nonreinforcement. *Journal of*

Experimental Psychology: Animal Behavior Processes, *12*(1), 4–15. doi:10.1037/0097-7403.12.1.4

Bouton, M. E., & Peck, C. A. (1989). Context effects on conditioning, extinction, and reinstatement in an appetitive conditioning preparation. *Animal Learning & Behavior*, *17*(2), 188–198. doi:10.3758/BF03207634

Bouton, M. E., Rosengard, C., Achenbach, G. G., Peck, C. A., & Brooks, D. C. (1993). Effects of contextual conditioning and unconditional stimulus presentation on performance in appetitive conditioning. *The Quarterly Journal of Experimental Psychology*, *46*(1), 63–95.

Cain, C. K., Godsil, B. P., Jami, S., & Barad, M. (2005). The L-type calcium channel blocker nifedipine impairs extinction, but not reduced contingency effects, in mice. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *12*(3), 277–284. doi:10.1101/lm.88805

Craske, M. G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., & Baker, A. (2008). Optimizing inhibitory learning during exposure therapy. *Behaviour Research and Therapy*, *46*(1), 5–27. doi:10.1016/j.brat.2007.10.003

Craske, M. G., Wolitzky-Taylor, K. B., Mineka, S., Zinbarg, R., Waters, A. M., Vrshek-Schallhorn, S., … Ornitz, E. (2012). Elevated responding to safe conditions as a specific risk factor for anxiety versus depressive disorders: evidence from a longitudinal investigation. *Journal of Abnormal Psychology*, *121*(2), 315–324. doi:10.1037/a0025738

Das, R. K., Kamboj, S. K., Ramadas, M., Yogan, K., Gupta, V., Redman, E., … Morgan, C. J. A. (2013). Cannabidiol enhances consolidation of explicit fear extinction in humans. *Psychopharmacology*, *226*(4), 781–792. doi:10.1007/s00213-012-2955-y

Deębiec, J., Doyère, V., Nader, K., & LeDoux, J. E. (2006). Directly reactivated, but not indirectly reactivated, memories undergo reconsolidation in the amygdala. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(9), 3428–3433. doi:10.1073/pnas.0507168103

Denniston, J. C., Chang, R. C., & Miller, R. R. (2003). Massive extinction treatment attenuates the renewal effect. *Learning and Motivation*, *34*(1), 68–86. doi:10.1016/S0023-9690(02)00508-8

Dirikx, T., Beckers, T., Muyls, C., Eelen, P., Vansteenwegen, D., Hermans, D., & D'Hooge, R. (2007). Differential acquisition, extinction, and reinstatement of conditioned suppression in mice. *Quarterly Journal of Experimental Psychology (2006)*, *60*(10), 1313–1320. doi:10.1080/17470210701515785

Dirikx, T., Hermans, D., Vansteenwegen, D., Baeyens, F., & Eelen, P. (2007). Reinstatement of conditioned responses in human differential fear conditioning. *Journal of Behavior Therapy and Experimental Psychiatry*, *38*(3), 237–251. doi:10.1016/j.jbtep.2006.04.001

Dirikx, T., Vansteenwegen, D., Eelen, P., & Hermans, D. (2009). Non-differential return of fear in humans after a reinstatement procedure. *Acta Psychologica*, *130*(3), 175–182. doi:10.1016/j.actpsy.2008.12.002

Dirikx, T. (2006). *Reinstatement of conditioned responding in humans and animals. An experimental investigation of differential return of fear (KU Leuven unpublished PhD dissertation)*.

Fonteyne, R., Vervliet, B., Hermans, D., Baeyens, F., & Vansteenwegen, D. (2010). Exposure to the context and removing the unpredictability of the US: two methods to reduce contextual anxiety compared. *Biological Psychology*, *85*(3), 361–369. doi:10.1016/j.biopsycho.2010.08.007

Frohardt, R. J., Guarraci, F. A., & Bouton, M. E. (2000a). The effects of neurotoxic hippocampal lesions on two effects of context after fear extinction. *Behavioral Neuroscience*, *114*(2), 227–240. doi:10.1037/0735-7044.114.2.227

Frohardt, R. J., Guarraci, F. A., & Bouton, M. E. (2000b). The effects of neurotoxic hippocampal lesions on two effects of context after fear extinction. *Behavioral Neuroscience*, *114*(2), 227–240.

Gazendam, F. J., & Kindt, M. (2012). Worrying Affects Associative Fear Learning: A Startle Fear Conditioning Study. *PLoS ONE*, *7*(4), e34882. doi:10.1371/journal.pone.0034882

Glenn, C. R., Lieberman, L., & Hajcak, G. (2012a). Comparing electric shock and a fearful screaming face as unconditioned stimuli for fear learning. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *86*(3), 214–219. doi:10.1016/j.ijpsycho.2012.09.006

Glenn, C. R., Lieberman, L., & Hajcak, G. (2012b). Comparing electric shock and a fearful screaming face as unconditioned stimuli for fear learning. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *86*(3), 214–219. doi:10.1016/j.ijpsycho.2012.09.006

Golkar, A., Bellander, M., & Öhman, A. (2013). Temporal properties of fear extinction--does time matter? *Behavioral Neuroscience*, *127*(1), 59–69. doi:10.1037/a0030892

Golkar, A., Bellander, M., Olsson, A., & Ohman, A. (2012). Are fear memories erasable?-reconsolidation of learned fear with fear-relevant and fear-irrelevant stimuli. *Frontiers in Behavioral Neuroscience*, *6*, 80. doi:10.3389/fnbeh.2012.00080

Golkar, A., & Öhman, A. (2012). Fear extinction in humans: effects of acquisition-extinction delay and masked stimulus presentations. *Biological Psychology*, *91*(2), 292–301. doi:10.1016/j.biopsycho.2012.07.007

Golkar, A., Selbing, I., Flygare, O., Ohman, A., & Olsson, A. (2013). Other People as Means to a Safe End: Vicarious Extinction Blocks the Return of Learned Fear. *Psychological Science*. doi:10.1177/0956797613489890

Grillon, C. (2002). Startle reactivity and anxiety disorders: aversive conditioning, context, and neurobiology. *Biological Psychiatry*, *52*(10), 958–975.

Grillon, C., Baas, J. M. P., Cornwell, B., & Johnson, L. (2006). Context conditioning and behavioral avoidance in a virtual reality environment: effect of predictability. *Biological Psychiatry*, *60*(7), 752–759. doi:10.1016/j.biopsych.2006.03.072

Haaker, J., Gaburro, S., Sah, A., Gartmann, N., Lonsdorf, T. B., Meier, K., … Kalisch, R. (2013). Single dose of L-dopa makes extinction memories context-independent and prevents the return of fear. *Proceedings of the National Academy of Sciences*, 201303061. doi:10.1073/pnas.1303061110

Haaker, J., Lonsdorf, T. B., Thanellou, A., & Kalisch, R. (2013). Multimodal Assessment of Long-Term Memory Recall and Reinstatement in a Combined Cue and Context Fear Conditioning and Extinction Paradigm in Humans. *PLoS ONE*, *8*(10), e76179. doi:10.1371/journal.pone.0076179

Hall, G. (1996). Learning about associatively activated stimulus representations: Implications for acquired equivalence and perceptual learning. *Animal Learning & Behavior*, *24*(3), 233–255.

Halladay, L. R., Zelikowsky, M., Blair, H. T., & Fanselow, M. S. (2012). Reinstatement of extinguished fear by an unextinguished conditional stimulus. *Frontiers in Behavioral Neuroscience*, *6*, 18. doi:10.3389/fnbeh.2012.00018

Harris, J. A., Jones, M. L., Bailey, G. K., & Westbrook, R. F. (2000). Contextual control over conditioned responding in an extinction paradigm. *Journal of Experimental Psychology. Animal Behavior Processes*, *26*(2), 174–185.

Hermans, D., Dirikx, T., Vansteenwegen, D., Vansteenwegenin, D., Baeyens, F., Van den Bergh, O., & Eelen, P. (2005). Reinstatement of fear responses in human aversive conditioning. *Behaviour Research and Therapy*, *43*(4), 533–551. doi:10.1016/j.brat.2004.03.013

Holland, P. C. (1981). Acquisition of representation-mediated conditioned food aversions. *Learning and Motivation*, *12*(1), 1–18. doi:10.1016/0023-9690(81)90022-9

Huff, N. C., Hernandez, J. A., Blanding, N. Q., & LaBar, K. S. (2009). Delayed Extinction Attenuates Conditioned Fear Renewal and Spontaneous Recovery in Humans. *Behavioral Neuroscience*, *123*(4), 834–843. doi:10.1037/a0016511

Kalisch, R., Korenfeld, E., Stephan, K. E., Weiskopf, N., Seymour, B., & Dolan, R. J. (2006). Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *26*(37), 9503–9511. doi:10.1523/JNEUROSCI.2021-06.2006

Kattoor, J., Gizewski, E. R., Kotsis, V., Benson, S., Gramsch, C., Theysohn, N., … Elsenbruch, S. (2013). Fear Conditioning in an Abdominal Pain Model: Neural Responses during Associative Learning and Extinction in Healthy Subjects. *PLoS ONE*, *8*(2), e51149. doi:10.1371/journal.pone.0051149

Kattoor, J., Thürling, M., Gizewski, E. R., Forsting, M., Timmann, D., & Elsenbruch, S. (2013). Cerebellar Contributions to Different Phases of Visceral Aversive

Extinction Learning. *Cerebellum (London, England)*. doi:10.1007/s12311-013-0512-9

Kellett, J., & Kokkinidis, L. (2004). Extinction deficit and fear reinstatement after electrical stimulation of the amygdala: implications for kindling-associated fear and anxiety. *Neuroscience*, *127*(2), 277–287. doi:10.1016/j.neuroscience.2004.05.011

Kim, J. H., & Richardson, R. (2007). A developmental dissociation in reinstatement of an extinguished fear response in rats. *Neurobiology of Learning and Memory*, *88*(1), 48–57. doi:10.1016/j.nlm.2007.03.004

Kindt, M., & Soeter, M. (2013a). Reconsolidation in a human fear conditioning study: a test of extinction as updating mechanism. *Biological Psychology*, *92*(1), 43–50. doi:10.1016/j.biopsycho.2011.09.016

Kindt, M., & Soeter, M. (2013b). Reconsolidation in a human fear conditioning study: a test of extinction as updating mechanism. *Biological Psychology*, *92*(1), 43–50. doi:10.1016/j.biopsycho.2011.09.016

Kindt, M., Soeter, M., & Vervliet, B. (2009). Beyond extinction: erasing human fear responses and preventing the return of fear. *Nature Neuroscience*, *12*(3), 256–258. doi:10.1038/nn.2271

Kull, S., Müller, B. H., Blechert, J., Wilhelm, F. H., & Michael, T. (2012). Reinstatement of fear in humans: autonomic and experiential responses in a differential conditioning paradigm. *Acta Psychologica*, *140*(1), 43–49. doi:10.1016/j.actpsy.2012.02.007

LaBar, K. S., & Phelps, E. A. (2005). Reinstatement of conditioned fear in humans is context dependent and impaired in amnesia. *Behavioral Neuroscience*, *119*(3), 677–686. doi:10.1037/0735-7044.119.3.677

Laurent, V., & Westbrook, R. F. (2010). Role of the basolateral amygdala in the reinstatement and extinction of fear responses to a previously extinguished conditioned stimulus. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *17*(2), 86–96. doi:10.1101/lm.1655010

Leweke, F. M., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C. W., Hoyer, C., … Koethe, D. (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational Psychiatry*, *2*, e94. doi:10.1038/tp.2012.15

Lissek, S., Powers, A., McClure, E., Phelps, E., Woldehawariat, G., Grillon, C., & Pine, D. (2005). Classical fear conditioning in the anxiety disorders: a meta-analysis. *BEHAVIOUR RESEARCH AND THERAPY*, *43*(11), 1391–1424. doi:10.1016/j.brat.2004.10.007

Lissek, S., Rabin, S., Heller, R. E., Lukenbaugh, D., Geraci, M., Pine, D. S., & Grillon, C. (2009). Overgeneralization of Conditioned Fear as a Pathogenic Marker of Panic Disorder. *Am J Psychiatry*. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19917595

Lissek, S., Rabin, S., Heller, R. E., Lukenbaugh, D., Geraci, M., Pine, D. S., & Grillon, C. (2010). Overgeneralization of conditioned fear as a pathogenic marker of panic disorder. *The American Journal of Psychiatry*, *167*(1), 47–55. doi:10.1176/appi.ajp.2009.09030410

Lonsdorf, T. B., Haaker, J., Fadai, T., & Kalisch, R. (2013). No evidence for enhanced extinction memory consolidation through noradrenergic reuptake inhibition-delayed memory test and reinstatement in human fMRI. *Psychopharmacology*. doi:10.1007/s00213-013-3338-8

Lonsdorf, T. B., Haaker, J., & Kalisch, R. (2014). Long-term expression of human contextual fear and extinction memories involves amygdala, hippocampus and ventromedial prefrontal cortex: a reinstatement study in two independent samples. *Social Cognitive and Affective Neuroscience*, nsu018. doi:10.1093/scan/nsu018

Maier, S., Szalkowski, A., Kamphausen, S., Perlov, E., Feige, B., Blechert, J., … Tüscher, O. (2012). Clarifying the role of the rostral dmPFC/dACC in fear/anxiety: learning, appraisal or expression? *PloS One*, *7*(11), e50120. doi:10.1371/journal.pone.0050120

Maren, S. (2011). Seeking a spotless mind: extinction, deconsolidation, and erasure of fear memory. *Neuron*, *70*(5), 830–845. doi:10.1016/j.neuron.2011.04.023

Maren, S., Phan, K. L., & Liberzon, I. (2013). The contextual brain: implications for fear conditioning, extinction and psychopathology. *Nature Reviews. Neuroscience*, *14*(6), 417–428. doi:10.1038/nrn3492

Marschner, A., Kalisch, R., Vervliet, B., Vansteenwegen, D., & Büchel, C. (2008). Dissociable Roles for the Hippocampus and the Amygdala in Human Cued versus Context Fear Conditioning. *The Journal of Neuroscience*, *28*(36), 9030 –9036. doi:10.1523/JNEUROSCI.1651-08.2008

Mechias, M.-L., Etkin, A., & Kalisch, R. (2010). A meta-analysis of instructed fear studies: implications for conscious appraisal of threat. *NeuroImage*, *49*(2), 1760–1768. doi:10.1016/j.neuroimage.2009.09.040

Milad, M. R., Orr, S. P., Pitman, R. K., & Rauch, S. L. (2005). Context modulation of memory for fear extinction in humans. *Psychophysiology*, *42*(4), 456–464. doi:10.1111/j.1469-8986.2005.00302.x

Milad, M. R., Wright, C. I., Orr, S. P., Pitman, R. K., Quirk, G. J., & Rauch, S. L. (2007). Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biological Psychiatry*, *62*(5), 446–454. doi:10.1016/j.biopsych.2006.10.011

Morris, R. W., Westbrook, R. F., & Killcross, A. S. (2005). Reinstatement of extinguished fear by beta-adrenergic arousal elicited by a conditioned context. *Behavioral Neuroscience*, *119*(6), 1662–1671. doi:10.1037/0735-7044.119.6.1662

Myers, K. M., & Davis, M. (2007). Mechanisms of fear extinction. *Molecular Psychiatry*, *12*(2), 120–150. doi:10.1038/sj.mp.4001939

Myers, K. M., Ressler, K. J., & Davis, M. (2006). Different mechanisms of fear extinction dependent on length of time since fear acquisition. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *13*(2), 216–223. doi:10.1101/lm.119806

Nader, K., Schafe, G. E., & Le Doux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval [see comments]. *Nature*, *406*(6797), 722.

Norrholm, S. D., Jovanovic, T., Vervliet, B., Myers, K. M., Davis, M., Rothbaum, B. O., & Duncan, E. J. (2006). Conditioned fear extinction and reinstatement in a human fear-potentiated startle paradigm. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *13*(6), 681–685. doi:10.1101/lm.393906

Norrholm, S. D., Vervliet, B., Jovanovic, T., Boshoven, W., Myers, K. M., Davis, M., … Duncan, E. J. (2008). Timing of extinction relative to acquisition: a parametric analysis of fear extinction in humans. *Behavioral Neuroscience*, *122*(5), 1016–1030. doi:10.1037/a0012604

Pavlov, IP. (1927). *Conditioned reflexes*. London: Oxford University Press.

Pearce, J. M., & Bouton, M. E. (2001). Theories of associative learning in animals. *Annual Review of Psychology*, *52*(1), 111–139.

Pearce, J. M., & Hall, G. (1980). A model for Pavlovian learning: Variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychological Review*, *87*(6), 532–552. doi:10.1037/0033-295X.87.6.532

Pineño, O., & Miller, R. R. (2004). Signaling a change in cue-outcome relations in human associative learning. *Learning & Behavior*, *32*(3), 360–375.

Quirk, G. J., & Mueller, D. (2008). Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *33*(1), 56–72. doi:10.1038/sj.npp.1301555

Rescorla, R. A. (1979). Conditioned inhibition and extinction. *Mechanisms of Learning and Motivation: A Memorial Volume to Jerzy Konorski*, 83–110.

Rescorla, R. A., & Cunningham, C. L. (1977). The erasure of reinstated fear. *Animal Learning & Behavior*, *5*(4), 386–394. doi:10.3758/BF03209584

Rescorla, R. A., & Heth, C. D. (1975). Reinstatement of fear to an extinguished conditioned stimulus. *Journal of Experimental Psychology. Animal Behavior Processes*, *1*(1), 88–96.

Rescorla, R., & Wagner, A. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In A. Black & W. Prokasy (Eds.), *Classical Conditioning II: Current Research and Theory* (pp. 64–99). Appleton-Century-Crofts.

Richardson, R., Duffield, T. Q., Bailey, G. K., & Westbrook, R. F. (1999). Reinstatement of fear to an extinguished conditioned context. *Animal Learning & Behavior*, *27*(4), 399–415. doi:10.3758/BF03209977

Richardson, R., Riccio, D. C., & Devine, L. (1984). ACTH-induced recovery of extinguished avoidance responding. *Physiological Psychology*, *12*(3), 184–192.

Schiller, D., Cain, C. K., Curley, N. G., Schwartz, J. S., Stern, S. A., Ledoux, J. E., & Phelps, E. A. (2008). Evidence for recovery of fear following immediate extinction in rats and humans. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *15*(6), 394–402. doi:10.1101/lm.909208

Schiller, D., Monfils, M.-H., Raio, C. M., Johnson, D. C., LeDoux, J. E., & Phelps, E. A. (2010). Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature*, *463*(7277), 49–U51. doi:10.1038/nature08637

Schmajuk, N. A., Larrauri, J. A., & Labar, K. S. (2007). Reinstatement of conditioned fear and the hippocampus: an attentional-associative model. *Behavioural Brain Research*, *177*(2), 242–253. doi:10.1016/j.bbr.2006.11.026

Sevenster, D., Beckers, T., & Kindt, M. (2012a). Instructed extinction differentially affects the emotional and cognitive expression of associative fear memory. *Psychophysiology*, *49*(10), 1426–1435. doi:10.1111/j.1469-8986.2012.01450.x

Sevenster, D., Beckers, T., & Kindt, M. (2012b). Retrieval per se is not sufficient to trigger reconsolidation of human fear memory. *Neurobiology of Learning and Memory*, *97*(3), 338–345. doi:10.1016/j.nlm.2012.01.009

Sevenster, D., Beckers, T., & Kindt, M. (2013). Prediction error governs pharmacologically induced amnesia for learned fear. *Science (New York, N.Y.)*, *339*(6121), 830–833. doi:10.1126/science.1231357

Soeter, M., & Kindt, M. (2010). Dissociating response systems: Erasing fear from memory. *Neurobiology of Learning and Memory*, *94*(1), 30–41. doi:10.1016/j.nlm.2010.03.004

Soeter, M., & Kindt, M. (2011). Disrupting reconsolidation: pharmacological and behavioral manipulations. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *18*(6), 357–366. doi:10.1101/lm.2148511

Sokol, N., & Lovibond, P. F. (2012). Cross-US reinstatement of human conditioned fear: return of old fears or emergence of new ones? *Behaviour Research and Therapy*, *50*(5), 313–322. doi:10.1016/j.brat.2012.02.005

Vervliet, B., Baeyens, F., Van den Bergh, O., & Hermans, D. (2013). Extinction, generalization, and return of fear: a critical review of renewal research in humans. *Biological Psychology*, *92*(1), 51–58. doi:10.1016/j.biopsycho.2012.01.006

Vervliet, B., Craske, M. G., & Hermans, D. (2013). Fear extinction and relapse: state of the art. *Annual Review of Clinical Psychology*, *9*, 215–248. doi:10.1146/annurev-clinpsy-050212-185542

Wade, S. L., Monroe, S. M., & Michelson, L. K. (1993). Chronic life stress and treatment outcome in agoraphobia with panic attacks. *The American Journal of Psychiatry*, *150*(10), 1491–1495.

Weike, A. I., Schupp, H. T., & Hamm, A. O. (2007). Fear acquisition requires awareness in trace but not delay conditioning. *Psychophysiology*, *44*(1), 170–180. doi:10.1111/j.1469-8986.2006.00469.x

Westbrook, R. F., Iordanova, M., McNally, G., Richardson, R., & Harris, J. A. (2002). Reinstatement of fear to an extinguished conditioned stimulus: two roles for context. *Journal of Experimental Psychology. Animal Behavior Processes*, *28*(1), 97–110.

Wilson, A., Brooks, D. C., & Bouton, M. E. (1995). The role of the rat hippocampal system in several effects of context in extinction. *Behavioral Neuroscience*, *109*(5), 828–836.

Woods, A. M., & Bouton, M. E. (2008). Immediate extinction causes a less durable loss of performance than delayed extinction following either fear or appetitive conditioning. *Learning & Memory*, *15*(12), 909–920. doi:10.1101/lm.1078508

Figures

Figure 1. Number of studies reporting significant reinstatement (RI) in the control group, no significant, differential or generalized RI, split up for different dependent measures.

Tables (provided at the end of the file)

Table 1. Reinstatement effects in different dependent measures in the included studies.

Table 2. Overview of reinstatement-specific experimental design specifications in human reinstatement studies.

Table 3. Overview of general sample and study characteristics in human reinstatment studies.

Table 4. Methodological recommendation for future studies.

Figure 1

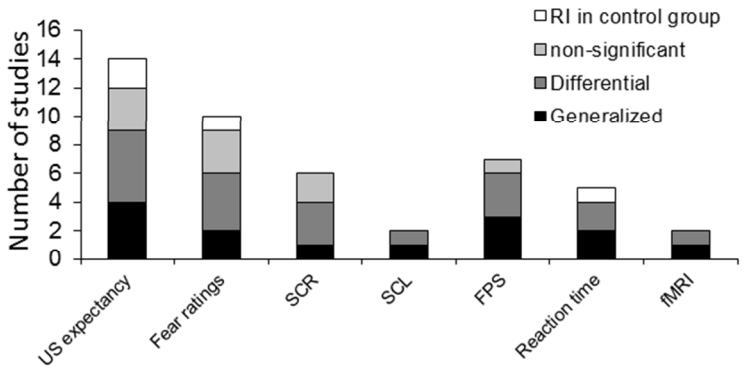
RI in control group
non-significant
Differential
Generalized
Number of studies
16
14
12
10
8
6
4
2
0
US expectancy
Fear ratings
SCR
SCL
FPS
Reaction time
fMRI

Table 1. Reinstatement effects in different dependent measures in the included studies.

	reinstatement group			control group (if applicable)
study	**Differential response enhancement (DR)**	**Generalized response enhancement (GR)**	**noresponse enhancement**	**significant response enhancement**
Dirikx 2004	• RT (a)	• Fear ratings (even though stronger for CS+) • US expectancy		• Fear ratings to CS+ #
Hermans 2005	• Fear ratings (a) • Reaction times • US expectancy			• Reaction times (DR)
Labar 2005 Exp 1 (SC)	• SCRs (, same context)		• SCRs (different context)	
Exp 2	• SCRs			
Milad 2005	• SCL (b)			
Norrholm 2006	• FPS (c) • US expectancy			
Dirkikx 2007	• US expectancy	• Fear ratings (but time x CS type x group interaction n.s.) • Reaction times		• US expectancy
Schiller 2008 (SC)	SCRs (single cue experiment)			
Dirikx 2009		• Fear ratings • US expectancy • RT (mainly driven by the CS-)		• US expectancy (mainly to the CS-)
Kull 2012	• US expectancy (trend: p= 0.07)	• US expectancy • SCRs		• US expectancy (GR) • SCRs (GR)
Golkar 2012a	• FPS (unmasked, delayed extinction group) (d) • FPS (masked, both delayed and immediate extinction) • US expectancy (unmasked, both delayed and immediate extinction) • US expectancy (masked, immediate extinction)	• US expectancy (masked , delayed extinction)	• FPS (unmasked, immediate extinction)	
Golkar 2012b		• FPS (irrespective of number of extinction trials)		

Sokol 2012		• SCL (for both same and different $US_{reinstatement}$ groups) • US expectancy (same-US group) (e) • US expectancy (different US group for new- US) (e)	• US expectancy (ratings for the $US_{acquisition}$ in the different $US_{reinstatement}$ group)	
Kattor 2013a	• parahippocampal activation at 0.001(uc) and 0.09 (SVC_{FWE})		• US expectancy	
Kattoor 2013b	• cerebellar activation (Crus I, lobule IX, right Crus II, right lobule I-IV and V)			
Kindt 2013	• US expectancy	• FPS • SCRs		
Gazendam 2012		• FPS • US expectancy (f)		
Sevenster 2012	• US expectancy (non-instructed extinction) • FPS (in non-instructed and instructed extinction group, though more pronounced on a descriptive level in the non-instructed extinction group)		• SCR (in instructed and non-instructed extinction group) • US expectancy (instructed extinction group) (g)	
Haaker 2013	• Fear ratings to contexts	• Fear ratings to contexts • FPS to Cues • SCRs to Cues and contexts	• Fear ratings to Cues • FPS to Cues	
Golkar 2013	• SCRs			
Lonsdorf 2014 Discovery sample		• SCRs to contexts • Ratings to Cues • dmPFC • amygdala – SCR correlation • anterior hippocampus	• SCRs to Cues • Ratings to contexts	
Replication sample		• SCRs to Cues and contexts • amygdala • anterior hippocampus	• Ratings to Cues and contexts	

(a) between reinstatement and control group only trendwise difference (in group x time x CS type ANOVA)
(b) significant for CS+, nonsignificant on descriptive level for CS-, but no stats for discrimination reported
(c) only reported for "extinguishers" at least 50% extinction
(d) also when testing extinguishes (50% criterion)
(e) no main effect of time is reported, but the graphs and the text suggest it
(f) no statistics reported but the graph suggests it
(g) no statistics reported and the graph suggests generalized reinstatement (only reported that it is not differential reinstatement)
DR: differential reinstatement
GR: generalized reinstatement
SC: single-cue experiment (thus no distinction between DR and GR possible)

statistical trend p<0.1

TABLE 2	Experimental timing in reinstatement					statistical calculation of reinstatement effects				
author	spatial contextual change	visual RI context	N RI UCS	Reinstatement phase timing	gap last reistatment US-first test trial	statistical test	factor phase *	analyses based on single trials or trial blocks	if block, number of trials per block	exclusion from the experiemnt due to other than technical problems
1 Dirikx (2004)	no		2	E--> rating --> (extra E trials if applicable)--> 5s --> US --> 5s--> US --> four reaction time task probes in a 50 sec time period (timing different in control and reinstatment group)--> RI test	50s	phase x CS type x group ANOVA	yes	single-trials	RT: 2 trials/ block (E) , 1 trial/block (RI), ratings: 4 trials/ block (E), 1 trial/block (RI)	unawares excluded
2 Hermans (2005)	no	cue background without cue (blank screen)	4	E--> 15s --> US --> 40s --> US --> 20s --> US --> 10 s --> instruction for test phase --> RI test	> 10s	phase x CS type x group ANOVA	yes	block	RT: 8 trials/ block (E) , 2 trial/block (RI), ratings: 12 trials/ block (E), 2 trial/block (RI)	unawares excluded
3 LaBar (2005) Exp.1	yes (a)	cue background without cue ("appropriate computer screen background as part of the context")	4	waiting room for 5 min --> reattachment of equipment in same or different context --> 4 US with intertrial interval of 50 ms --> waiting room for 5 min --> reattachment of equipment in original context	> 5min	phase x [*group*] ANOVA	yes	single-trials		
Exp. 2	no		4			phase x CS type ANOVA	yes	single trials		
4 Milad (2005)	yes (b)	conditioning context	2	renewal test --> conditioning context for 18s --> US conditioning context for 18s --> US --> immediately thereafter RI test		phase ANOVA seperately for CS types	yes	single-trials	1 trial	no measurable change in SCL to any trial during conditioning (N=11)
5 Norrholm (2006)	no		3	E --> 19 s --> US US US (duration of this phase unclear) --> 18s --> RI test	18s	phase x CS type ANOVA)	yes	blocks (FPS)	4	exclude non extinguishers (50%) for FPS
6 Dirikx (2007)	no	cue background without cue (black screen)	2	E--> 5s --> US --> 5s--> US --> four reaction time task probes in a 50 sec time period (timing different in control and RI group)--> RI test	5s	phase x CS type x group ANOVA	yes	block	RT: 8 trials/ block (E) , 2 trial/block (RI), ratings: 4 trials/ block (E), 2 trial/block (RI)	unawares excluded
7 Schiller (2008)	yes (a)	1) cue background without cue 2) different background	4	24h after E four presentations of the US, with a 50-sec ITI	24h	phase x [*group*] ANOVA	yes	single-trials		unawares and unextinguishers excluded
8 Dirikx (2009)	no		2	E--> rating --> (extra E trials if applicable)--> all three CS in random order (with or without RT probes) --> 15.5s --> RT probe --> 11s --> US --> 7s --> RT probe --> 7s --> RT probe --> 12 s --> US --> 6.5s --> RT probe --> 1s --> RI test	7.5s	phase x CS type x group ANOVA	yes	blocks: RT single trials: ratings	RT: 2 trials/block	unawares excluded
9 Sevenster (2012a)	no		3	E --> US US US --> RI test		phase x [*group*] ANOVA	yes	single trials		none
10 Kull (2012)	no	blank screen with white fixation cross	3	approximately 70s duration during which three unpredicted USs for 0.5 s each were presented with ITIs of 16 to 20 s		phase x CS type x group ANOVA	yes	blocks	all trials	

11	Golkar (2012)	no	neutral (black screen)	3	E --> 11sec --> US US US --> 15sec --> RI test	15sec	phase x CS type [*x group*] ANOVA)	yes	single trials (ratings) blocks (FPS)	FPS: 2 probes/block	none
12	Sokol (2012)	no	white screen (as in ITI)	3			phase x CS type ANOVA	yes	single-trials		differences score >0 in final trial of conditioning for SCL and US expecancy
13	Gazendam (2012)	no		1	E --> unclear time gap--> US --> 17 sec ITI --> ITI startle probe --> RI test	17sec	phase x CS type x [group] ANOVA	yes	blocks	2 trials/block	failure to comply to instructions (N=21)
14	Kattoor (2013a)	no	"off phase screen" (white fame on black background)	1			ANOVA in RI test phase fMRI: CS+ vs. CS- in RI test phase	no	ratings: blocks fMRI: blocks	ratings: whole phase fmri: 6 each CS type	
15	Kattoor (2013b)	no	"off phase screen" (white fame on black background)	1			ANOVA in RI test phase fMRI: CS+ vs. CS- in RI test phase	no	ratings: blocks fMRI: blocks	ratings: whole phase fmri: 6 each CS type	
16	Kindt & Soeter (2013)	no		3	re-E trial ---> 19sec --> US US US --> 18sec --> RI test	18sec	phase x CS type x [*group*] ANOVA	yes	blocks (FPS) blocks/single trial (SCRs) single trials (ratings)	FPS: 2 probes/block SCR: 2 trials/block (E), 1 trial/block (RI)	insuffiecient FPS discrimination (N=9 in control group) for FPS analyses
17	Haaker (2013)	no	neutral (grey screen)	3	re-E --> ratings --> 5s--> US US US (5s interval between USs)--> 2min--> ratings --> reinstatment test	2min	phase x CS type ANOVA	yes	blocks (FPS, SCR) single trials (Ratings)	contexts: 3 trials/block cues: 6 trials/block	none
18	Lonsdorf (2014d)	no	neutral (grey screen)	3	re-E --> ratings --> 5s--> US US US (5s interval between USs)--> 2min--> ratings --> RItest	2min	phase x CS type ANOVA	yes	blocks (FPS, SCR, fmri) single trials (Ratings),	contexts: 3 trials/block cues: 6 trials/block fmri: all trials/phase	none
19	Golkar (2013)	no	neutral (black screen)	3	E-->13 sec--> US US US --> 30sec --> RI test	30sec	phase x CS type x group ANOVA	yes	blocks	FPS: 2 probes/block	
20	Golkar (2013)	no	neutral (black screen)	3	E --> black screen for 20s --> US US US --> 30sec--> RI test	30sec	[*group*] x CS type in RI test phase	no	block	3	

a reinstatment in same or differnt room
b Conditioing in CXT A, Extinciton in CXT B, extinction recall in CXT B, renewal in CXT A, reinstatment in CXT A

E Extinction
RI Reinstatement

empty cells represent missing information

TABLE 3

	author	conditioning type	experimental timing	reinforcement ratio	US type	CS type	N CS+/ N CS-	Number of trials: C (CS+/CS-)	Number of trials: E (CS+/CS-)	Number of trials: RI (CS+/CS-)	Instruction: A	Instruction: E	number of participants: RI group(s)	number of participants: Control group	number of participants: male: female	number of participants: unaware	number of participants: age (yrs)	dependent measurements: SCR/SCL	dependent measurements: FPS	dependent measurements: Ratings	dependent measurements: other
1	Dirikx (2004)	differential	single day (C,E, RI)	100%	electrotactile	faces[#]	1/3	8/8,8,8	12/12,12,12[%]	2/2	yes (a1)	no	17	16	19:14	13				US, Fear, Val	RT
2	Hermans (2005)	differential	single day (C,E, RI)	100%	electrotactile	faces[#]	1/1	12/12	36/36	2/2	yes (a1)	no	14	14	0:28	2				US, Fear, Val	RT
3	LaBar (2005) Exp. 1	single-cue	single day (C,E, $RI_{context}$)	100%	100dB sound	blue square	1/0	4	8	8	no	no	20 AAAA 23 AABA	none	15:28		range 18-22	SCR			
	Exp. 2	differential	single day (C,E, RI)	100%	100dB sound	red and green squares	1/1	4/4	8/8	8,8	no	no	27	none	11:16		range 18-22	SCR			
4	Milad (2005)	differential	2 days^ day 1: C,E day 2: E, E-RE, RN, RI	100%	electrotactile	2 rooms, 2 colored lights	1/1	5/5	10/10 or none	5/5	yes (c)	reminder (d)	20	none	20:21		mean 25.7	SCL			
5	Norrholm (2006)	differential	2 days day 1: C day 2: E, RI	75%	airblast	colored lights	1/1	16/16	24/24	4,4	yes (a2)	reminder (d)	22	22	20:25		mean 29.4			US	
6	Dirikx (2007)	differential	single day (C,E, RI)	100%	electrotactile	faces[#]	1/3	8/8,8,8	12/12,12,12	2 ,2	yes (a1)	no	16	17	RI: 1:15 control: 2:15	11	mean: 18,61			US, Fear, Val	RT
7	Schiller (2008)	single-cue	3 days day 1: C, E day 2: RI US day 3: $RI_{context}$	100%	electrotactile	fractale image	1/0	8	16	20	yes (c)	no	18 AAAA 16 AABA	none	16:18	6	range 18-27	SCR			
8	Dirikx (2009)	differential	single day (C,E, RI)	100%	electrotactile	faces[#]	1/2	8/8,8	12/12,12[%]	2 ,2	yes (a2)	yes	21	21		6				US, Fear, Val	RT
9	Sevenster (2012a)	differential	day 1:C day 2: E (instructed vs. non-instructed), RI	66,6%	electrotactile	blue square, yellow circle	1/1	6/6	16/16	8,8	yes (a2)	yes (N=24), no (N=25)	40	none	9:31		mean 21.75	SCR		US	
10	Kull (2012)	differential	single day (C,E, RI)	75%	electrotactile	neutral faces (both sexes)	1/1	4/4	6/6	2, 2	yes (a1)	yes	28	27	13:42	0	mean 25.2	SCR		US	
11	Golkar (2012)	differential	single day (C, E, RI) or 2 days day 1: C day 2: extinction	82%	electrotactile	fearful face - background color pairs	2/2	9,9/9,9	12,12,/12,12	4, 4, 4, 4,	yes (c)	no	27	none	8:19		mean 24.9			US	
12	Sokol (2012)	differential	single day (C, E, RI)	100%	electrotactile or acustic	different coloured squares	1/2	3/3,3	6/6,6	1 x A; 1 x B	NA	NA	82		34:48		mean 19.41	SCL		US expectancy	

13	Gazendam (2012)	differential	single day (C, E, RI)	75%	electrotactile	brown circle, grey square	1/1	8/8	12/12	6/6	yes (c)	no	48	none	Worry:4:19; no worry:7:18		mean 22.2			US expectancy (but nor for RI)	
14	Kattoor (2013a)	differential	single day (C, E, RI)	75%	abdom. pain	white geometric symbols in a white fame on black screen	1/1	16/16	12/12	6/6			21	none	15:6		mean 24.06			US,tens, val	BOLD
15	Kattoor (2013b)	differential	single day (C, E, RI)	75%	abdom. pain	white geometric symbols in a white fame on black screen	1/1	16/16	12,12	6/6			30[§]	none	15:15		mean 24.53				BOLD for cerebellum
16	Kindt & Soeter (2013)	differential	3 days day1: conditioning day 2: extinction day 3: re-extinction, reinstatement	75%	shock	pictures of spiders	1/1	8/8	12/12	8/8	yes (b+c)	reminder (d)	*	none	13:27		range 18–33	SCR		US	
17	Haaker (2013)	differential	3 days day1: C day 2: E day 3: RE-E, RI	100%, 0% and unpredictable[$]	electrotactile	pictures of living rooms, geometric symbols	$	9 each CXT; 18 each Cue	exinction and re-extinction each 6 each CXT, 12 each Cue	6 each CXT, 12 each Cue	no	no	93	none	23:70	19	range 20-46	SCR		Fear	
18	Lonsdorf (2014)	differential	3 days day1: C day 2: E day 3: RE-E, RI	100%, 0% and unpredictable[$]	electrotactile	pictures of living rooms, geometric symbols	$	9 each CXT; 18 each Cue	exinction and re-extinction each 6 each CXT, 12 each Cue	6 each CXT, 12 each Cue	no	no	20 (sample 1) 19 (sample 2)	none	39:0	sample1: 5; sample2: 3	mean: 29.0	SCR		Fear	BOLD
19	Golkar (2013)	differential	single day (C, E, RI)	67%	electrotactile	2 fearful male faces	1/1	9/9	12/12 or 24/24	4/4	yes (a2)	no	57		38:19	0	mean: 24				
20	Golkar (2013)	differential	single day (C, E, RI)	67%	electrotactile	2 angry male faces	1/1	6/6	6/6	6/6	yes (c)	no	Extinction groups: direct : (N=20); vicarious (N=16), vicarious reinf. (N=19)	none	55:0	4	mean 25.2	SCR			

LEGEND

C Conditioniong
E Extinction
E-RE Extinction Recall
RN Renewal
RI US presentation
RI Reinstatement Test
$RI_{context}$ Reinstatement Test with and without contextual change
RA Re-acquisition
^ Conditioing in CXT A, Extinciton in CXT B, extinction recall in CXT B, renewal in CXT A, reinstatment in CXT A
# selected individually to be neutral

three different conditions: predictable with 100% reinforcement of the discrete cue but 0% for the context, unpredictable with unpredictable US presentations mainly during the context and rarely

$ during the cue and a safe condition (no US to either cue or context)

% add further 8 extinction trials for each CS if not fully extinguished

a1 one stimulus will always be followed by the US

a2 one out of two will be sometimes/most of the time followed by the US

b a picture

c participants instructed to look for contingencies

d remember what you have learned/ you may or may not be shocked

§ sample overlaps with the sample in Kattoor et al. (2013a)

* unclear as only the control group is considered here (not specified)

empty cells represent missing information

Table 4. Methodological recommendation for future studies

Design:

- Include an extinction or additional extinction (re-extinction) phase right before the reinstatement manipulation to allow for a clean measure of reinstatement un-confounded by sensitization or other ROF processes (i.e. spontaneous recovery effects).
- To obtain a clean measure of reinstatement, consider that any contextual change during or after reinstatement may induce renewal processes and employ appropriate control groups.
- Consider the use of additional and appropriate control stimuli to allow disentangling of reinstatement from other ROF processes.
- It is highly recommended to use appropriate control groups (e.g. no reinstatement US control group and other controls depending on the specific experimental design).
- Include exact descriptions of the type of visual stimulation, other experimental phases (e.g. ratings) and timing during reinstatement-US administration.
- Prefer multimodal assessment of reinstatement effects.
- Carefully control for sequence effects following the reinstatement manipulation and report CS sequences in detail.
- Appreciate that US-recalibrations in multiple-day paradigms likely induce reinstatement effects.
- Acquire data on anxiety-related traits.
- Acquire data on CS-US awareness.
- Consider the role of instructions with respect to CS-US contingencies and report in detail.

Data analysis:

- Calculate reinstatement effects using a repeated measures design with time, CS-type (and possibly group) and provide all statistical information to facilitate comparison between different studies.
- Report results for both CS+ and CS- in differential conditioning protocols.
- Include a graphical display based on single-trials following reinstatement for all measurement modalities.
- In case participants are excluded (e.g. based on CS-US unawareness) report if results remain the same when including them.